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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,639	07/20/2001	Daniel A. Vallera	09531-023001 / Z01015	2607

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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,639	VALLERA ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-39* is/are pending in the application.

4a) Of the above claim(s) *1-17,19,25 and 30-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20,21 and 23, 24, and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the amendment filed 10/23/03 wherein the specification was amended; claims 18 and 23 were amended; and claim 22 was canceled. Also, Applicant complied with the sequence rules.

Note: Claims 1-21 and 23-29 are pending.

WITHDRAWN CLAIMS

2. Claims 1-17, 19, 25, and 30-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species (for explanation see the office action mailed 6/18/03).

RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS

3. The Applicant's arguments filed 10/23/03 to the rejection of claims 18, 20-24, and 26-29 made by the Examiner under 35 USC 102, 103, 112, and/or double patenting have been fully considered and deemed persuasive-in-part for the reasons set forth below.

Double Patenting Rejections

The double patenting rejection is WITHDRAWN for reasons of record in Applicant's response.

112 First Paragraph Rejections

The 112, first paragraph, rejections are WITHDRAWN for reason of record in Applicant's response.

112 Second Paragraph Rejections

I. The 112, second paragraph, rejection of claims 18, 20, 21, and 26-29 regarding it being unclear what pathogenic cell disease(s) the claims are directed to is WITHDRAWN because Applicant has clarified the claims.

II. The rejection of claims 18, 20, 21, 23, and 24 as being ambiguous because it is unclear what method Applicant is claiming is compatible with the instant invention is MAINTAINED. Specifically, the rejection has not been overcome because Applicant has not clarified what method the claims are directed to. Is Applicant's claim a method of treating cancer; a method of radiolabeling cancer; a method of identifying a type of cancer, etc. The claim as written is directed to 'a method' but does not set for what that method is.

102 Rejections

The 102 rejection is WITHDRAWN because Applicant has amended the claims to overcome the rejection (e.g, incorporated that the subject is suspected of having cancer).

103 Rejections

Both of the 103 rejections are WITHDRAWN because Applicant has amended the claims to overcome the rejection (e.g, incorporated that the subject is suspected of having cancer).

COMMENTS/NOTES # 1

4. Applicant is reminded of the election without traverse of Group III (claims 18-29) as set forth in the paperwork filed 3/31/03. Group III is directed to a method of administering a radiolabeled immunotoxin. Since the election was made without traverse the restriction requirement is deemed proper and is therefore made FINAL. Likewise, it is noted that Applicant elected a species wherein the toxic domain is diphtheria toxin; the targeting molecule is Her-2/Neu; and the radionuclide species is 64Cu.

Notes: Initially, Applicant's elected species was searched. However, since no prior art was found which could be used to reject the claims, the search was expanded to diphtheria toxin (toxic domain), any radionuclide, and anti-CD3 sFv (targeting moiety). *The search was not further expanded because prior art was found which could be used to reject Applicant's claims.*

NEW GROUNDS OF REJECTIONS

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 18, 20, 21, 23, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vallera et al (Blood, 1996, pages 2342-2353) in view of Neville et al

(US Patent No. 6,103,235) and in further view of Goldenberg (US Patent No. 5,332,567).

Vallera et al disclose anti-graft versus host disease (GVHD) effect of diphtheria toxin 390 (DT-390) antiCD3sFv, a single chain Fv fusion immunotoxin that specifically targets the CD3 epsilon moiety of the T-cell receptor (see entire document). In addition, Vallera et al disclose (1) mice received 2 micrograms of immunotoxin on a daily basis for six days (see abstract; page 2345, 'Fusion toxin administration'; page 2349 'Effect of DT390-anti-CD3sFv administration on in vivo GVHD'). (2) The immunotoxin was radiolabeled with 125I (page 2345, 'Pharmacokinetics'; page 2350, Figure 8). However, Vallera et al fail to disclose other methods wherein an immunotoxin is administered to a subject. In addition, Vallera et al fail to disclose other possible radionuclides which may be conjugated to the DT-390-anti-CD3sFv complex.

Neville et al disclose methods of inducing immune tolerance using immunotoxins. The immunotoxins comprise a mutant diphtheria toxin moiety linked to an antibody moiety. The immunotoxins are useful in treating graft-versus-host disease(see entire document, especially, abstract; column 2, lines 32-52; columns 4-5, bridging paragraph; column 6, lines 17-26; column 6, lines 45-47; columns 9-10, bridging paragraph). In addition, Neville et al disclose that their immunotoxin treatment is given by intraperitoneal injection when the tumor is visibly established (columns 2-3, bridging paragraph; columns 11-12, bridging paragraph). The mutant diphtheria toxin moiety may be truncated 9e.g., DT390, DT383, DT370, etc.) or full length toxins with point mutations (e.g., DTM1). The antibody portion of the immunotoxin may be

scUCHT1 or other anti-CD3 antibodies. One example of an immunotoxin for use in the experiments of Neville et al is UCHT1-DT390 (column 6, lines 17-26). In columns 21-25, Example 9, Neville et al disclose an anti-CD3 single chain immunotoxin having a truncated diphtheria toxin. Experiments were conducted with radiolabeled UCHT1-CRM9. This construct is made with a monoclonal antibody of mouse origin (UCHT1) and a binding site mutant of diphtheria toxin (CRM9) [column 21, lines 46-47 and column 22, lines 2-4]. The immunotoxin was radiolabeled with 125I (column 23, line 57; column 24, line 4; column 25, line 4).

Goldenberg discloses the detection, imaging, and treatment of infections using immunoconjugates comprising and antibody conjugate (see entire document, especially, abstract). The immunoconjugates comprise an immunoreactive component having at least one substantially monospecific antibody or antibody fragment conjugated to at least one diagnostic or therapeutic agent, wherein the antibody fragment binds to an epitope of the pathogen or of a pathogen-associated antigen (column 2, lines 47-55). The invention of Goldenberg also resolves many of the problems involved in the treatment of infections that are refractive to conventional drug therapy by using very specific antibodies against microbial or parasitic antigens in order to target an effective radionuclide and/or chemical agent resulting in selective killing of the pathogen (column 3, lines 41-47). The immunoconjugates are also effective diagnostic agents for scintigraphic imaging or magnetic resonance imaging of infection sites which enable a treating physician to evaluate a patients level and stage of infection and design and monitor treatment protocols (column 3, lines 59-64). The imaging agents may comprise

bispecific, trispecific, or polyspecific antibody/antibody fragment conjugates that optionally comprise an imaging radioisotope or paramagnetic species (column 4, lines 62-66).

Also, Goldenberg discloses the value of conjugating antibodies with radioisotopes and/or drugs or toxins to achieve target detection, imaging, and therapy of infection (column 6, lines 57-61; column 10, lines 7-26; column 13, lines 18-22; column 16, lines 5-45; column 19-28). The immunoconjugates may be labeled with metals such as Dy, Gd, or Mn to name a few (column 11, lines 6-23; column 18, lines 17-25). The methods and compositions of Goldenberg are effective in the treatment of acquired immune deficiency syndrome and similar conditions (column 18, lines 48-57; column 19, lines 30-35).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Vallera et al using the teachings of Neville et al and Goldenberg and use a radiolabeled immunotoxin in various methods and conjugate various radionuclides to the DT-390-antiCD3sFv complex because (a) both Vallera et al and Goldenberg disclose the use of immunoconjugates for targeting a diagnostic or therapeutic agent such as detecting, imaging, or treating and infection. (b) Goldenberg discloses that the immunoconjugate may be labeled with different radioisotopes depending upon the technique used (e.g., imaging, therapy, etc.). (c) Both Vallera et al and Neville et al disclose that their immunotoxins are useful for graft versus host disease (GVHD) and both may be radiolabeled. Thus, it would be obvious to a skilled person in the art to combine the teachings of the documents and generate

and immunotoxin comprising a radionuclide, toxic domain (DT-390) and a sFv antibody since both documents disclose toxin-containing conjugates. Also, it should be noted that the immunotoxins of Neville et al (column 3, lines 7-9) are administered to tumor containing subjects. Hence, a skilled practitioner using any standard medical dictionary (e.g., The Harper Collins Illustrated Medical Dictionary) would recognize that a cancer encompasses various types of tumor. A 'cancer' is defined as a *malignant tumor*. A 'tumor' is defined as a neoplasm or an overgrowth of tissue. A neoplasm is defined as the abnormal multiplication of cells within the formation of a mass or new growth of tissue which may be localized (benign) or spreading and invasive (malignant). Thus, a skilled practitioner in the art would be motivated to use an immunoconjugate for diseased tissue (i.e., malignant tumor), abnormal growth of localized tissue, or normal tissue as the immunoconjugate of Vallera et al which was administered to 'normal' mice.

Thus, since the references all disclose immunoconjugates containing toxins, the references may be considered to be within the same field of endeavor. Hence, the reference teachings are combinable.

COMMENTS/NOTES # 2

7. It should be noted that no prior art has been cited against claim 24. Claim 24 is distinguished over the prior art of record because the prior art neither anticipates nor renders obvious an immunotoxin comprising diphtheria toxin, 64Cu, and Her-2/Neu (Applicant's elected species). However, Applicant MUST address and overcome the 112 rejection(s) cited against the claim.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

January 8, 2004